FILE 'USPAT' ENTERED AT 16:33:30 ON 29 OCT 1997

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*    WELCOME TO THE         *
*  U.S. PATENT TEXT FILE    *
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=> s regulat? (2a) complement (2a) activat?
     266862 REGULAT?
      36053 COMPLEMENT
     351963 ACTIVAT?
L1       20 REGULAT? (2A) COMPLEMENT (2A) ACTIVAT?

=> s cr1 or cr2 or mcp or daf or c4bp or (factor h)
       3336 CR1
       2622 CR2
       1118 MCP
        408 DAF
         23 C4BP
     234059 FACTOR
     565534 H
        741 FACTOR H
            (FACTOR(W)H)
L2     5841 CR1 OR CR2 OR MCP OR DAF OR C4BP OR (FACTOR H)

=> s l2 (p) complement
      36053 COMPLEMENT
L3      131 L2 (P) COMPLEMENT

=> d

1. 5,679,546, Oct. 21, 1997, Chimeric proteins which block complement
activation; Jone-Long Ko, et al., 435/69.2, 69.7, 252.3, 320.1; 530/350,
412; 536/23.4 :IMAGE AVAILABLE:

=> d bib date ab


US PAT NO:   5,679,546 :IMAGE AVAILABLE:        L3: 1 of 131
DATE ISSUED: Oct. 21, 1997
TITLE:       Chimeric proteins which block complement activation
INVENTOR:    Jone-Long Ko, Sudbury, MA
             C. Grace Yeh, Marlborough, MA
ASSIGNEE:    Cytomed, Inc., Cambridge, MA (U.S. corp.)
APPL-NO:     08/310,416
DATE FILED:  Sep. 22, 1994
ART-UNIT:    182
PRIM-EXMR:   Stephen Walsh
ASST-EXMR:   Karen E. Brown
LEGAL-REP:   Fish & Richardson P.C.

                                L3: 1 of 131
TITLE:       Chimeric proteins which block complement activation
US PAT NO:   5,679,546          DATE ISSUED: Oct. 21, 1997
             :IMAGE AVAILABLE:
APPL-NO:     08/310,416         DATE FILED:  Sep. 22, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 126,596, Sep. 24, 1993,
             abandoned.
```


ABSTRACT:
The present invention relates to novel chimeric proteins comprising a first polypeptide which inhibits complement activation, linked to a second polypeptide which inhibits complement activation, nucleic acids encoding novel chimeric proteins and methods of reducing inflammation with the administration of the chimeric proteins of the invention.


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=> d clms

US PAT NO:   5,679,546 :IMAGE AVAILABLE:        L3: 1 of 131
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CLAIMS:

CLMS(1)

What is claimed is:

1. A soluble chimeric protein comprising a first soluble polypeptide which inhibits complement activation linked to a second soluble polypeptide which inhibits complement activation, wherein said first and second polypeptides are derived from the same or different member of the regulator of complement activation (RCA) family and wherein said first polypeptide is linked to said second polypeptide by a peptide bond.

CLMS(2)

2. The chimeric protein of claim 1, wherein said first polypeptide is derived from membrane cofactor protein, and said second polypeptide is derived from decay accelerating factor.

CLMS(3)

3. The chimeric protein of claim 1, wherein the members of the regulator of **complement** activation (RCA) family are selected from the group consisting of membrane cofactor protein, decay accelerating factor, **complement** receptor 1, **factor** **H**, and C4b binding protein.

CLMS(4)

4. The chimeric protein of claim 3, wherein said first and said second polypeptides are different.

CLMS(5)

5. The chimeric protein of claim 4, wherein the first polypeptide comprises a fragment of membrane cofactor protein and the second polypeptide comprises a fragment of decay accelerating factor.

CLMS(6)

6. The chimeric protein of claim 5, wherein said first polypeptide comprises at least regions 2, 3 and 4 of membrane cofactor protein short consensus repeats, and said second polypeptide comprises at least regions 2, 3 and 4 of decay accelerating factor short consensus repeats.

CLMS(7)

7. A nucleic acid encoding the chimeric protein of claim 1.

CLMS(8)

8. A recombinant expression vector comprising a selectable marker and the nucleic acid of claim 7 operably linked to regulatory sequences for expression of said protein.

CLMS(9)

9. The recombinant expression vector of claim 8, wherein said regulatory sequences comprise a mammalian promoter.

CLMS(10)

10. The expression vector of claim 8, wherein said selectable marker comprises a gene encoding glutamine synthetase or a gene encoding dihydrofolate reductase.

CLMS(11)

11. A process for preparing a recombinant chimeric protein, comprising culturing a suitable host cell comprising the vector of claim 8 under conditions promoting expression and purifying said protein from said cell.

CLMS(12)

12. The process of claim 11, wherein said host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

CLMS(13)

13. The process of claim 12, wherein said mammalian cell is a chinese hamster ovary cell.

CLMS(14)

14. The process of claim 11, further comprising, following said culturing step:
(a) collecting a cell supernatant or a cell lysate of said host cell;
(b) removing acid-precipitable contaminants from said supernatant or lysate to yield a partially-purified composition;
(c) contacting said composition with an anion exchange resin to bind said chimeric protein thereto and then eluting said chimeric protein;
(d) removing metal-binding contaminants from said chimeric protein;
(e) binding said chimeric protein to a phenyl hydrophobic interaction resin and then eluting said chimeric protein;
(f) binding said chimeric protein to a butyl hydrophobic interaction resin and then eluting said chimeric protein; and
(g) removing endotoxin from said chimeric protein, wherein steps d.-f. can be carried out in any order.

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=> d his

    (FILE 'USPAT' ENTERED AT 16:33:30 ON 29 OCT 1997)
L1       20 S REGULAT? (2A) COMPLEMENT (2A) ACTIVAT?
L2     5841 S CR1 OR CR2 OR MCP OR DAF OR C4BP OR (FACTOR H)
L3      131 S L2 (P) COMPLEMENT

=> s l1 or l3
L4      136 L1 OR L3

=> s (fusion or chimer? or hybrid) and l4
      37853 FUSION
       2603 CHIMER?
      33101 HYBRID
L5       91 (FUSION OR CHIMER? OR HYBRID) AND L4

=> s (fusion or chimer? or hybrid) (p) l4
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37853 FUSION
2603 CHIMER?
33101 HYBRID
L6 9 (FUSION OR CHIMER? OR HYBRID) (P) L4

=> d bib date ab 1-

US PAT NO: 5,679,546 :IMAGE AVAILABLE: L6: 1 of 9
DATE ISSUED: Oct. 21, 1997
TITLE: Chimeric proteins which block complement activation
INVENTOR: Jone-Long Ko, Sudbury, MA
C. Grace Yeh, Marlborough, MA
ASSIGNEE: Cytomed, Inc., Cambridge, MA (U.S. corp.)
APPL-NO: 08/310,416
DATE FILED: Sep. 22, 1994
ART-UNIT: 182
PRIM-EXMR: Stephen Walsh
ASST-EXMR: Karen E. Brown
LEGAL-REP: Fish & Richardson P.C.

L6: 1 of 9
TITLE: Chimeric proteins which block complement activation
US PAT NO: 5,679,546 DATE ISSUED: Oct. 21, 1997
:IMAGE AVAILABLE:
APPL-NO: 08/310,416 DATE FILED: Sep. 22, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 126,596, Sep. 24, 1993, abandoned.

ABSTRACT:
The present invention relates to novel chimeric proteins comprising a first polypeptide which inhibits complement activation, linked to a second polypeptide which inhibits complement activation, nucleic acids encoding novel chimeric proteins and methods of reducing inflammation with the administration of the chimeric proteins of the invention.

US PAT NO: 5,643,770 :IMAGE AVAILABLE: L6: 2 of 9
DATE ISSUED: Jul. 1, 1997
TITLE: Retroviral vector particles expressing complement inhibitor activity
INVENTOR: James M. Mason, Wallingford, CT
Stephen P. Squinto, Bethany, CT
ASSIGNEE: Alexion Pharmaceuticals, Inc., New Haven, CT (U.S. corp.)
APPL-NO: 08/278,630
DATE FILED: Jul. 21, 1994
ART-UNIT: 185
PRIM-EXMR: Mindy Fleisher
ASST-EXMR: Johnny F. Railey, II
LEGAL-REP: Seth A. Fidel, Maurice M. Klee

L6: 2 of 9
TITLE: Retroviral vector particles expressing complement inhibitor activity
US PAT NO: 5,643,770 DATE ISSUED: Jul. 1, 1997
:IMAGE AVAILABLE:
APPL-NO: 08/278,630 DATE FILED: Jul. 21, 1994

ABSTRACT:
Modified retroviral vector particles and modified retroviral producer cells producing such particles are provided for facilitating gene therapy procedures involving the transduction of target cells with retroviral vector particles in the presence of complement containing body fluids. The modifications involve genetic alterations to effect the expression by these cells and particles of complement inhibitor activity. The genetic alterations involve the introduction of nucleic acid expression constructs directing the expression of retroviral SU(gp70)/complement inhibitor chimeric proteins into cells from which the producer cells are derived.

US PAT NO: 5,627,264 :IMAGE AVAILABLE: L6: 3 of 9
DATE ISSUED: May 6, 1997
TITLE: Chimeric complement inhibitor proteins
INVENTOR: William L. Fodor, New Haven, CT
Scott Rollins, Monroe, CT
Stephen P. Squinto, Bethany, CT
ASSIGNEE: Alexion Pharmaceuticals, Inc., New Haven, CT (U.S. corp.)
APPL-NO: 08/205,508
DATE FILED: Mar. 3, 1994
ART-UNIT: 184
PRIM-EXMR: Robert A. Wax
ASST-EXMR: Kawai Lau
LEGAL-REP: Seth A. Fidel, Maurice M. Klee

L6: 3 of 9
TITLE: Chimeric complement inhibitor proteins
US PAT NO: 5,627,264 DATE ISSUED: May 6, 1997
:IMAGE AVAILABLE:
APPL-NO: 08/205,508 DATE FILED: Mar. 3, 1994

ABSTRACT:
Chimeric complement inhibitor proteins are provided which include a first functional domain (first amino acid sequence) having C3 inhibitory activity and a second functional domain (second amino acid sequence) having C5b-9 inhibitory activity. The first functional domain is amino terminal to the second functional domain. In this way, the chimeric protein exhibits both C3 and C5b-9 inhibitory activity. The other orientation, i.e., the orientation in which the second amino acid sequence is amino terminal to the first amino acid sequence, only produces C3 inhibitory activity. Nucleic acid molecules encoding such proteins are also provided.

US PAT NO: 5,624,837 :IMAGE AVAILABLE: L6: 4 of 9
DATE ISSUED: Apr. 29, 1997
TITLE: Nucleic acid encoding chimeric complement inhibitor proteins
INVENTOR: William L. Fodor, New Haven, CT
Scott Rollins, Monroe, CT
Stephen P. Squinto, Bethany, CT
ASSIGNEE: Alexion Pharmaceuticals, Inc., New Haven, CT (U.S. corp.)
APPL-NO: 08/458,084
DATE FILED: Jun. 1, 1995
ART-UNIT: 184
PRIM-EXMR: Robert A. Wax
ASST-EXMR: Kawai Lau
LEGAL-REP: Seth A. Fidel, Maurice M. Klee

L6: 4 of 9
TITLE: Nucleic acid encoding chimeric complement inhibitor proteins
US PAT NO: 5,624,837 DATE ISSUED: Apr. 29, 1997
:IMAGE AVAILABLE:
APPL-NO: 08/458,084 DATE FILED: Jun. 1, 1995
REL-US-DATA: Division of Ser. No. 205,508, Mar. 3, 1994.

ABSTRACT:
Chimeric complement inhibitor proteins are provided which include a first functional domain (first amino acid sequence) having C3 inhibitory activity and a second functional domain (second amino acid sequence) having C5b-9 inhibitory activity. The first functional domain is amino terminal to the second functional domain. In this way, the chimeric protein exhibits both C3 and C5b-9 inhibitory activity. The other orientation, i.e., the orientation in which the second amino acid sequence is amino terminal to the first amino acid sequence, only produces C3 inhibitory activity. Nucleic acid molecules encoding such proteins are also provided.

US PAT NO: 5,545,619 :IMAGE AVAILABLE: L6: 5 of 9
DATE ISSUED: Aug. 13, 1996
TITLE: Modified complement system regulators
INVENTOR: John P. Atkinson, St. Louis, MO
Dennis Hourcade, Creve Coeur, MO
Malgorzata Krych, St. Louis, MO
ASSIGNEE: Washington University, St. Louis, MO (U.S. corp.)
APPL-NO: 08/210,266
DATE FILED: Mar. 18, 1994
ART-UNIT: 182
PRIM-EXMR: Stephen G. Walsh
LEGAL-REP: Arnall Golden & Gregory

L6: 5 of 9
TITLE: Modified complement system regulators
US PAT NO: 5,545,619 DATE ISSUED: Aug. 13, 1996
:IMAGE AVAILABLE:
APPL-NO: 08/210,266 DATE FILED: Mar. 18, 1994
REL-US-DATA: Continuation of Ser. No. 695,514, May 3, 1991, abandoned.

ABSTRACT:
Analogs of regulators of complement activation (RCA) proteins which have altered specificities and affinities for the targets C3b and/or C4b are described. These analogs are obtained by substituting amino acids which effect the binding of these proteins, identified as amino acids 35, 64-65, 92-94 (C4b) and the sequence S-T-K-P-(P-I-C)-Q (SEQ ID NO:1) (C3b) in the CR1 protein can be transferred to corresponding regions of CR1 or of additional members of the RCA family. Analogs can also be designed by substituting amino acids which affect the binding of these proteins into homologous regions of noncorresponding SCRs of CR1 or other family members.

US PAT NO: 5,472,939 :IMAGE AVAILABLE: L6: 6 of 9
DATE ISSUED: Dec. 5, 1995
TITLE: Method of treating complement mediated disorders
INVENTOR: Douglas T. Fearon, Baltimore, MD
Lloyd B. Klickstein, Brookline, MA
Winnie W. Wong, Newton, MA
Gerald R. Carson, Wellesley, MA
Michael F. Concino, Newton, MA
Stephen H. Ip, Sudbury, MA
Savvas C. Makrides, Bedford, MA
Henry C. Marsh, Jr., Reading, MA
ASSIGNEE: The Johns Hopkins University, Baltimore, MD (U.S. corp.)
The Brigham and Women's Hospital, Boston, MA (U.S. corp.)

T Cell Sciences, Inc., Needham, MA (U.S. corp.)
APPL-NO: 08/138,825
DATE FILED: Oct. 19, 1993
ART-UNIT: 182
PRIM-EXMR: Garnette D. Draper
ASST-EXMR: John D. Ulm
LEGAL-REP: Pennie & Edmonds

L6: 6 of 9

TITLE: Method of treating complement mediated disorders
US PAT NO: 5,472,939 DATE ISSUED: Dec. 5, 1995
:IMAGE AVAILABLE:
APPL-NO: 08/138,825 DATE FILED: Oct. 19, 1993
REL-US-DATA: Division of Ser. No. 588,128, Sep. 24, 1990, Pat. No. 5,256,642, which is a continuation-in-part of Ser. No. 412,745, Sep. 26, 1989, abandoned, which is a continuation-in-part of Ser. No. 332,865, Apr. 3, 1989, Pat. No. 5,212,071, which is a continuation-in-part of Ser. No. 176,532, Apr. 1, 1988, abandoned.

ABSTRACT:
The present invention relates to the C3b/C4b receptor (CR1) gene and its encoded protein. The invention also relates to CR1 nucleic acid sequences and fragments thereof comprising 70 nucleotides and their encoded peptides or proteins comprising 24 amino acids. The invention further provides for the expression of the CR1 protein and fragments thereof. The genes and proteins of the invention have uses in diagnosis and therapy of disorders involving complement activity, and various immune system or inflammatory disorders. In specific embodiments of the present invention detailed in the examples sections infra, the cloning, nucleotide sequence, and deduced amino acid sequence of a full-length CR1 cDNA and fragments thereof are described. The expression of the CR1 protein and fragments thereof is also described. Also described is the expression of a secreted CR1 molecule lacking a transmembrane region. The secreted CR1 molecule is shown to be useful in reducing damage caused by inflammation and in reducing myocardial infarct size and preventing reperfusion injury.

US PAT NO: 5,256,642 :IMAGE AVAILABLE: L6: 7 of 9
DATE ISSUED: Oct. 26, 1993
TITLE: Compositions of soluble complement receptor 1 (CR1) and a thrombolytic agent, and the methods of use thereof
INVENTOR: Douglas T. Fearon, Baltimore, MD
Lloyd B. Klickstein, Brookline, MA
Winnie W. Wong, Newton, MA
Gerald R. Carson, Wellesley, MA
Michael F. Concino, Newton, MA
Stephen H. Ip, Sudbury, MA
Savvas; C. Makrides, Bedford, MA
Henry C. Marsh, Jr., Reading, MA
ASSIGNEE: The Johns Hopkins University, Baltimore, MD (U.S. corp.)
Brigham and Women's Hospital, Boston, MA (U.S. corp.)
T Cell Sciences, Inc., Cambridge, MA (U.S. corp.)
APPL-NO: 07/588,128
DATE FILED: Sep. 24, 1990
ART-UNIT: 184
PRIM-EXMR: Robert A. Wax
ASST-EXMR: Stephen Walsh
LEGAL-REP: PenniPenni

L6: 7 of 9

TITLE: Compositions of soluble complement receptor 1 (CR1) and a thrombolytic agent, and the methods of use thereof
US PAT NO: 5,256,642 DATE ISSUED: Oct. 26, 1993
:IMAGE AVAILABLE:
APPL-NO: 07/588,128 DATE FILED: Sep. 24, 1990
REL-US-DATA: Continuation-in-part of Ser. No. 412,745, Sep. 26, 1989, abandoned, which is a continuation-in-part of Ser. No. 332,865, Apr. 3, 1989, abandoned, which is a continuation-in-part of Ser. No. 176,532, Apr. 1, 1988, abandoned.

ABSTRACT:
The present invention relates to compositions comprising soluble complement receptor 1 (CR1) and a thrombolytic agent. In a specific embodiment, the thrombolytic agent is anisoylated human plasminogen-streptokinase activator complex (ASPAC). The invention further relates to methods for treating thrombotic conditions in humans and animals by administering a composition comprising soluble CR1 and a thrombolytic agent. In particular, the compositions and methods are useful both for reducing reperfusion injury and ameliorating the other effects of myocardial infarction.

US PAT NO: 5,252,216 :IMAGE AVAILABLE: L6: 8 of 9
DATE ISSUED: Oct. 12, 1993
TITLE: Protein purification
INVENTOR: Gail Folena-Wasserman, Richboro, PA
John H. O'Grady, King of Prussia, PA
Thomas M. Smith, Drexel Hill, PA
John Lifter, Wellesley, MA
ASSIGNEE: SmithKline Beecham Corporation, Philadelphia, PA (U.S. corp.)
APPL-NO: 07/857,022
DATE FILED: Mar. 24, 1992
ART-UNIT: 136
PRIM-EXMR: Ernest G. Therkorn
LEGAL-REP: Herbert H. Jervis, Edward T. Lentz, Stuart R. Suter

L6: 8 of 9

TITLE: Protein purification
US PAT NO: 5,252,216 DATE ISSUED: Oct. 12, 1993
:IMAGE AVAILABLE:
APPL-NO: 07/857,022 DATE FILED: Mar. 24, 1992

ABSTRACT:
This invention relates to the application of combination chromatography to the purification of complement receptor proteins.

US PAT NO: 5,212,071 :IMAGE AVAILABLE: L6: 9 of 9
DATE ISSUED: May 18, 1993
TITLE: Nucleic acids encoding a human C3b/C4b receptor (CR1)
INVENTOR: Douglas T. Fearon, Baltimore, MD
Lloyd B. Klickstein, Brookline, MA
Winnie W. Wong, Newton, MA
Gerald R. Carson, Wellesley, MA
Michael F. Concino, Newton, MA
Stephen H. Ip, Sudbury, MA
Savvas C. Makrides, Bedford, MA
ASSIGNEE: The Johns Hopkins University, Baltimore, MD (U.S. corp.)
Brigham and Women's Hospital, Boston, MA (U.S. corp.)
T Cell Sciences, Inc., Cambridge, MA (U.S. corp.)
APPL-NO: 07/332,865
DATE FILED: Apr. 3, 1989
ART-UNIT: 182
PRIM-EXMR: David L. Lacey
ASST-EXMR: John D. Ulm

L6: 9 of 9

TITLE: Nucleic acids encoding a human C3b/C4b receptor (CR1)
US PAT NO: 5,212,071 DATE ISSUED: May 18, 1993
:IMAGE AVAILABLE:
APPL-NO: 07/332,865 DATE FILED: Apr. 3, 1989
REL-US-DATA: Continuation-in-part of Ser. No. 176,532, Apr. 1, 1988, abandoned.